Neutral Citation Number: [2019] EWHC 1085 (Pat)

Case Nos: HP-2017-000079, HP-2018-000009

IN THE HIGH COURT OF JUSTICE
BUSINESS AND PROPERTY COURTS
INTELLECTUAL PROPERTY LIST (CHANCERY DIVISION)
PATENTS COURT

Rolls Building
Fetter Lane, London, EC4A 1NL

Date: 3 May 2019

Before :

MR JUSTICE ARNOLD

- -

Between :

(1) ALLERGAN, INC	**Claimants**
(2) ALLERGAN LIMITED	
- and -	
ASPIRE PHARMA LIMITED	**Defendant**

And between :

ACCORD HEALTHCARE LIMITED	**Claimant**
- and -	
ALLERGAN, INC	**Defendant**

- -
- -

Henry Ward and **Isabel Jamal** (instructed by **Bird & Bird LLP**) for **Allergan**
Thomas Hinchliffe QC and **Katherine Moggridge** (instructed by **Innovate Legal** and **Pinsent Masons LLP**) for **Aspire** and **Accord**

Hearing dates: 9-12, 16 April 2019

- -

Approved Judgment

I direct that pursuant to CPR PD 39A para 6.1 no official shorthand note shall be taken of this Judgment and that copies of this version as handed down may be treated as authentic.

.....

MR JUSTICE ARNOLD

MR JUSTICE ARNOLD :

Contents

Introduction

1. Allergan, Inc is the proprietor of European Patent (UK) No. 1 753 434 entitled "Enhanced bimatoprost ophthalmic solution" ("the Patent"). Allergan Ltd is a subsidiary of Allergan, Inc which exploits the Patent in the UK by marketing a product containing 0.1 mg/ml (0.01%) bimatoprost for ophthalmic administration for the treatment of glaucoma under the trade mark Lumigan 0.1 mg/ml. This replaced an

earlier product called Lumigan 0.3 mg/ml that contained 0.3 mg/ml (0.03%) bimatoprost. In essence, the invention claimed in the Patent is a formulation containing a lower concentration of bimatoprost (in particular 0.01%, rather than 0.03%) and a higher concentration of a preservative called benzalkonium chloride ("BAK") (in particular, 200 ppm or 0.02% rather than 50 ppm or 0.005%).

2. Aspire Pharma Ltd and Accord Healthcare Ltd ("the Defendants") have obtained marketing authorisations to market generic versions of Lumigan 0.1 mg/ml. For the purposes of these proceedings, the Defendants do not dispute that dealings in their respective intended products would infringe the Patent. The Defendants contend that the Patent is invalid on the ground that the claimed inventions were obvious over Laibovitz *et al*, "Comparison of the Ocular Hypotensive Lipid AGN 192024 with Timolol", *Arch. Ophthalmol.*, 119(7), 994-1000 (2001) ("Laibovitz"), alternatively insufficient. There is no challenge to the claimed priority date of 16 March 2005. Allergan, Inc and Allegan Ltd (collectively "Allergan") have applied unconditionally to amend the Patent to add a new claim 18. The amendment application is only opposed on the ground that it does not cure the alleged obviousness of the Patent.

The witnesses

3. Allergan and the Defendants each called two expert witnesses, an ophthalmologist and a formulator. In addition, Allergan called a single factual witness.

The ophthalmologists

4. Allergan's ophthalmologist was Dr Jeremy Diamond. He obtained an MBChB from the University of Bristol in 1984 and a PhD from the same institution in 1995. He became a Fellow of both the Royal College of Surgeons and the Royal College of Ophthalmologists in 1990. He has been a Consultant Ophthalmologist at the Bristol Eye Hospital ("BEH") since 1996. He was the first glaucoma Consultant at the BEH and established the glaucoma department. Over much of the last 22 years he has been responsible for managing the department. Mr Diamond also established the Clinical Research Unit at the BEH. He has been involved in running a number of Phase III clinical trials, including those for a number of prostaglandins for the treatment of glaucoma. He has published over 50 articles and book chapters, including 17 glaucoma-related research papers in peer-reviewed journals.

5. As counsel for the Defendants rightly accepted, Dr Diamond was a good witness who did his best to assist the Court. There was little between him and Prof Morgan after cross-examination.

6. The Defendants' ophthalmologist was Professor James Morgan. He obtained a BA in Medicine Sciences from Downing College, Cambridge in 1982, a DPhil from St John's College, Oxford in 1986 and an MB BCH from Green College, Oxford in 1992. He became a Fellow of the Royal College of Ophthalmologists in 1992. He has been a Consultant Ophthalmologist at Cardiff University since 1997 and successively Senior Lecturer (from 1997 to 2003), Reader (from 2003 to 2009) and Professor of Ophthalmology at the same institution (since 2009). He chaired the UK and Eire Glaucoma Society in 2007. He was seconded to Moorfields Eye Hospital in London as Chief Information Officer from 2014 to 2016. He spends just under half of his time doing clinical work, providing direct patient care including glaucoma services. He has

had a specialist research interest in glaucoma for many years and has published numerous papers in the field.

7. Counsel for Allergan criticised Prof Morgan for omitting one point in his discussion of Laibovitz in his reports. As counsel for the Defendants pointed out, however, the same criticism can be levelled at Dr Diamond. In any event, Prof Morgan readily accepted the point when it was put to him. In my view Prof Morgan was another good witness.

The formulators

8. Allergan's formulator was Professor Uday Kompella. He has been a Professor in the Departments of Pharmaceutical Sciences (primary) and Ophthalmology at the University of Colorado, Denver since 2008. Prof Kompella received a BPharm degree from BITS, Pilani, India in 1987, an MPharm (Pharm Eng) from Jadavpur University, Kolkata, India in 1989 and a PhD in Pharmaceutical Sciences from the University of Southern California in 1994. The focus of his PhD was ophthalmic formulation development for drug delivery enhancement across ocular tissues, including conjunctiva and cornea. He briefly worked developing nasal spray formulations after his PhD, but by autumn 1994 he had joined Auburn University School of Pharmacy as a faculty member. In 2005 he became a tenured Associate Professor at the University of Nebraska, with a joint appointment in the Department of Ophthalmology. He has published over 200 articles and book chapters on ophthalmic formulation and drug delivery.

9. Counsel for the Defendants submitted that Prof Kompella was an unsatisfactory witness. I regret to have to say that I agree with this. Prof Kompella was evasive in many of his answers. At first, I thought that this might be because he was concerned to be scientifically accurate in the light of his current knowledge, but he continued in the same vein even after I had explained to him that what mattered was the skilled formulator's common general knowledge in March 2005. As his cross-examination continued, Prof Kompella resorted with increasing frequency to saying that he could not comment on propositions that were being put to him. He even declined to comment on whether the use of 100 ppm BAK would require invention.

10. Perhaps of most concern was the fact that, in his second report, Prof Kompella relied upon a paper by Camber and Edman ("Factors influencing the corneal permeability of prostaglandin F2α and its isopropyl ester in vitro", *Int J Pharmaceutics*, 37, 27-32 (1987)) as showing that BAK would be likely to inhibit, rather than enhance, the corneal permeability of a lipophilic drug like bimatoprost. As Prof Alany explained in his third report, however, Prof Kompella had misinterpreted Camber and Edman since the key conclusion is that the corneal epithelium functions as a barrier for hydrophilic drugs and as the site of activation through hydrolysis of pro-drugs such as prostaglandin F2α esters, and not that BAK inhibits the penetration of lipophilic drugs. Prof Alany's explanation of Camber and Edman was not challenged in cross-examination, and counsel for Allergan accepted in closing submissions that it was correct. Despite this, Prof Kompella did not retract his comments about Camber and Edman in his evidence in chief, and it required a lengthy passage of cross-examination and an intervention by myself before he accepted Prof Alany's analysis.

11. The Defendants' formulator was Professor Raid Alany. He has been Professor of Pharmaceutical Formulation and Drug Delivery at Kingston University, London since 2017. He obtained an MSc in Pharmaceutical Chemistry from University of Baghdad, Iraq in 1992 and a PhD in ocular drug delivery from the University of Otago, New Zealand, in 2001. In the same year, he became a Lecturer at the School of Pharmacy, University of Auckland, where he was responsible for establishing the first Pharmaceutics curriculum. He was promoted to Senior Lecturer in 2004, to Head of Pharmaceutics in 2007 and to Senior Lecturer above the bar (equivalent to Reader) in 2009. In 2011 he became Professor of Pharmaceutics at Kingston University. In 2013 he was appointed as the Research Director for the School of Pharmacy and Chemistry. He served as Inaugural Head of the School of Life Sciences, Pharmacy and Chemistry from 2015 to 2017. Prof Alany's research mainly relates to ophthalmic drug delivery. He has published over 100 articles and book chapters and co-authored a book.

12. As counsel for the Defendants submitted, the contrast between Prof Alany and Prof Kompella was striking. Prof Alany gave clear and cogent answers to questions, even though his task was made harder by the length and complexity of some of those questions. Accordingly, I consider that his evidence is to be preferred to that of Prof Kompella where they conflict.

13. Counsel for Allergan submitted that Prof Alany's evidence was tainted by hindsight, because he was aware of the Lumigan 0.1 mg/ml product before his involvement in this case as a result of writing an editorial he had been asked to write which was published in 2013. It was not put to Prof Alany, however, that he had been aware that Lumigan 0.1 mg/ml contained a higher level of BAK than Lumigan 0.3 mg/ml. Counsel for Allergan relied upon Prof Alany's acceptance that he would have been interested in differences from a formulation perspective between the new product and the old product, but that does not show that he was in fact aware of the BAK levels. Moreover, Prof Alany made it clear that he did not have much recollection of the editorial. In any event, it is the cogency of Prof Alany's reasons that matter.

Factual witness

14. Dr Chin-Ming Chang was employed by Allergan, Inc from 1999 to 2018. From 1999 to 2007 he worked as a formulator first as a Senior Scientist and then Principal Scientist, Formulation Development. He was CMC (Chemistry, Manufacturing and Controls) Subteam Leader of Allergan's Lumigan Enhancement Project from May 2003 until its completion. This project led to the development of Lumigan 0.1 mg/ml. Dr Chang is one of the five named inventors of the Patent. Dr Chang is no longer employed by Allergan and gave evidence by video-link from Taiwan, where he is now based.

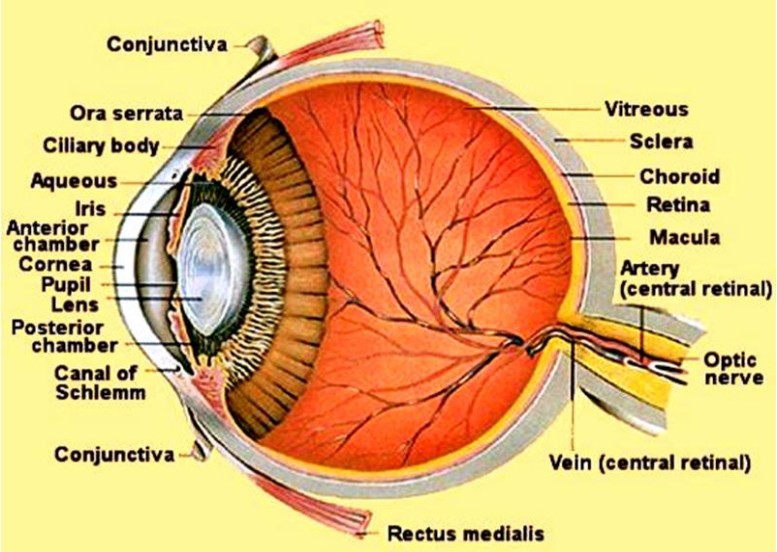
15. Dr Chang fairly accepted that his recollection of the Lumigan Enhancement Project was poor and that his evidence was mainly based on the documents. As he explained, the documents annexed to his witness statement had been selected by Allergan's solicitors. As such, his evidence was guided by that selection of documents. Counsel for the Defendants submitted that the documents showed that Dr Chang had misunderstood an important aspect of the timeline concerning the Project. Counsel for Allergan disputed that the Defendants' case on the timing was correct, but had to accept that the position was unclear because the key document had not been disclosed by Allergan. In any event, Dr Chang had no involvement in the earlier stages of the

Project prior to May 2003 and therefore could not speak to those. Even after May 2003, it appears that he had little personal involvement in the work leading to the claimed invention. Thus Scott Jordan did the formulation work, while Joan-En Chang-Lin (who still works for Allergan) was the scientist who carried out the studies which form the basis for the Examples in the Patent. This is significant for the reason explained below.

Technical background

The eye

16. A cross-section of the human eye is shown in the diagram below.



17. The pre-ocular area consists of two main structures (not shown in the diagram): the tear film and the nasolacrimal apparatus. The tear film covers and lubricates the cornea, conjunctiva and sclera. Tear fluid is spread over the surface of the eye during blinking. It drains through the lacrimal drainage system which connects the front of the eye with the back of the nose and the gastrointestinal tract.

18. The eye comprises the following ocular membranes:

    i) The conjunctiva: a thin, transparent, highly vascular, mucous membrane which lines the inner surface of the eyelid and folds back to cover the anterior surface of the eye, including the exterior of the sclera, except for the cornea.

    ii) The cornea: a transparent dome shape covering the front of the eyeball. It represents one-sixth of the total surface area of the eyeball. It is an important mechanical barrier, which protects the intraocular tissues. It is generally understood to be the primary route of entry for delivering topically applied drugs to the intra-ocular tissues. The cornea is composed of five layers (from outside to inside):

        a) A stratified epithelium. The epithelium regenerates continually and has the ability to heal rapidly without scarring in the event of injury. The cells of the epithelium are encircled by tight junctions and consist of

five to six cell layers: a single basal layer, the two to three layers above comprising wing cells and the outermost two layers of squamous surface cells. The epithelium is a hydrophobic layer. Its hydrophobicity means that it accounts for 90% of the barrier to hydrophilic drug entry to the eye and roughly 10% for hydrophobic drugs.

b) Bowman's layer (or membrane). This lies behind the epithelium and is composed of a layer of collagen fibres which form a relatively tight and impermeable barrier against microorganisms and protect the stroma.

c) The stroma. This is approximately 90% of the corneal thickness. It is mainly composed of regularly arranged layers of hydrated collagen fibrils. Its hydrophilicity means that it is the main barrier of entry to the eye for hydrophobic drugs.

d) Descemet's membrane. This is comprised of collagen fibres arranged in a fine latticework pattern.

e) The corneal endothelium. This is a single layer of flattened polygonal cells. It plays an important role in the maintenance of corneal hydration and transparency.

iii) The sclera. This is the white part of the eye. It is a protective barrier for the sensitive inner parts and is composed of the same type of collagen fibres as the stroma.

19. The anterior chamber of the eye is the fluid-filled space behind the cornea. It contains aqueous humour, a transparent watery liquid which bathes the structures of the eye in front of the lens, including the lens' anterior surface. Aqueous humour is produced by epithelial cells of the ciliary body. The main function of aqueous humour is to provide nutrition to the surrounding structures and to maintain the eye's intra-ocular pressure ("IOP") which in turn helps to maintain the shape of the eye. The fine balance between aqueous production and outflow determines IOP. IOP can vary as a result of several factors, including time of day, heartbeat and age, but in general terms most individuals will have an IOP value of between 10 and 21 mm Hg.

20. Aqueous humour fills the tiny posterior chamber behind the iris and flows through the pupil into the anterior chamber where it then drains out of the eye by one of two routes. In humans up to 70% outflows through the trabecular network and the canal of Schlemm into the conjunctival veins and the systemic circulation. This is known as conventional drainage. The remaining 30% of aqueous humour drains through the unconventional (uveoscleral) pathway via the stroma and vessels of the iris root and ciliary body. Unlike conventional drainage, which is pressure sensitive, the unconventional route occurs regardless of the IOP.

Drug delivery to the eye

21. There are three main routes via which drugs are administered to the eye: topical, systemic and by intra-ocular injection. The latter two routes are not relevant for present purposes.

22. Topically applied drugs ultimately exert their effect on the tissues bathed by aqueous humour. To do so, they must enter the eye. The main route of drug entry was understood in 2005 to be through the cornea. Thus the more a drug permeates through the cornea, the greater the concentration of drug in the aqueous humour. It was also understood, however, that non-corneal routes of absorption may be significant for drug molecules with poor corneal permeability. For example, the ophthalmic drug timolol had been reported to gain comparable intra-ocular access by the conjunctival/scleral route and the corneal route.

23. Topical application usually involves the administration of eye drops (although it may involve gels or ointments). A large part of eye drops is wasted. Only a small amount of the dose (somewhere between 1 and 10%) typically reaches the internal structures of the eye. This is mainly due to spillage and rapid drainage via the nasolacrimal pathway, but also due to the hydrophilic/lipophilic barriers of the cornea, the pH of the ophthalmic solution, and metabolism of the drug in the pre-ocular area.

24. Drugs penetrate the corneal epithelium via two routes: transcellular (through the cells) and paracellular (round or between the cells). Lipophilic drugs prefer the transcellular route, whereas hydrophilic drugs penetrate primarily through the paracellular pathway. There was no settled consensus as to the optimum partition coefficient (i.e. degree of lipophilicity) for corneal permeation in March 2005: it had been variously reported to be in the range of logP 1 to 2, 2 to 3 and 1 to 3.

Glaucoma

25. The term "glaucoma" refers to a group of eye diseases characterised by optic nerve damage leading to progressive visual loss, particularly affecting the field of vision. Disruption of outflow of aqueous humour results in increased IOP, which in turn, over time, causes damage to the optic nerve. If left untreated, glaucoma may cause blindness. The risk of glaucoma increases with age, particularly over the age of 40.

26. The most common form of glaucoma is primary open angle glaucoma ("POAG"). It is usually asymptomatic until it is at an advanced stage, at which point irreversible visual loss has occurred. It is therefore important that, once diagnosed, patients with POAG are closely monitored and treated to avoid permanent damage to their vision.

27. As glaucoma is associated with an increased resistance to the outflow of aqueous humour, which raises IOP, a primary risk factor in the development of glaucoma is an IOP of greater than 21 mm Hg. Although the IOP threshold for nerve damage varies between individuals (some of whom might have damage below the 21 mm Hg threshold, or conversely may not suffer damage despite being above it), the majority of patients with glaucoma will have an IOP of greater than 21 mm Hg at some point during the course of their disease. A consistently elevated IOP above 21mm Hg, in the absence of other signs of glaucoma, is described as ocular hypertension.

28. Due to this relationship between elevated pressure and risk of glaucoma, all of the available treatments in 2005 focused on reducing IOP to a level which minimised damage to the optic nerve. In general terms, this can be achieved by either reducing the production of aqueous humour or by increasing the outflow of aqueous humour from the eye.

29. The target pressure is assessed for each patient based on a number of factors. These include the severity of the current disease and their age. The aim is to maintain IOP at or below the target for that patient. It was generally accepted in 2005 that, other things being equal, IOP should be lowered as much as practically possible, but there was no benchmark for "ideal" IOP reduction. Moreover, it was recognised that, because of side effects and other issues, an agent that had maximal IOP lowering effect was not necessarily the right agent for a particular patient.

30. A reduction in IOP of 20% or more was generally regarded as a good clinical response, although for some patients a greater reduction, of 30% or more, was required.

Adherence/compliance

31. Glaucoma is a chronic condition. Lack of patient adherence with treatment (often described as "compliance" in the literature) was in March 2005 (and remains) an important issue when treating glaucoma. As explained above, glaucoma is asymptomatic until late in the disease, when the patient notices a change in their vision. By this point, loss of vision is usually significant. The aim of the treatment therefore is to limit disease progression in order to preserve vision, as opposed to controlling symptoms. Drug therapy may be needed for the rest of the patient's life. Patient education about glaucoma and the need for treatment adherence is therefore very important. The skilled ophthalmologist in 2005 would generally have considered anything which improved patient adherence with a treatment regime to be of clinical benefit.

32. In general, most patients are less diligent with their therapy than they claim. Whilst it is difficult to determine the rate of non-adherence precisely, it was reported to be in the range of 28-58% of patients.

33. There are many factors which influence patient adherence to therapy. These include:

    i) the patient's perception of the disease;

    ii) how complex or inconvenient the dosing regimen is;

    iii) practical reasons, such as difficulty in using the medication bottle correctly; and

    iv) the effects of the drops (including side effects).

Glaucoma drugs

34. The initial treatment of glaucoma is usually by means of medication, although IOP may also be lowered surgically or by laser treatment.

35. In March 2005 the main classes of drugs used to lower IOP were:

    i) Beta-blockers. These were discovered in the 1960s and reduce IOP by decreasing the rate of secretion of aqueous humour. 10% of the population are unresponsive to beta-blockers. They are also associated with significant systemic side effects. These systemic adverse effects include bradycardia and

respiratory effects such as bronchospasm. Despite these risks, before the introduction of latanoprost in 1997, the majority of patients were treated with a beta-blocker. Even after prostaglandin analogues ("PGAs") became available, the beta-blocker timolol was still one of the main topical treatments used in March 2005 as it typically lowered IOP by 20-25%. Thus timolol was generally regarded as the standard against which to compare new treatments. Another beta-blocker, betaxolol, was less effective in reducing IOP than timolol, but had the advantage that it had fewer side effects.

ii) Carbonic anhydrase inhibitors. These became available in the mid-1990s and lowered IOP by inhibiting the secretion of aqueous humour. The most commonly available carbonic anhydrase inhibitor in 2005 was dorzolamide, but it was not as efficacious as timolol. The prime benefit of this class was that they lacked the systemic side effects of non-selective beta-blockers.

iii) PGAs. These were introduced in 1997. PGAs lower IOP by increasing the outflow of aqueous humour from the eye. In March 2005, the following PGAs were available for the treatment of glaucoma in the UK:

a) latanoprost 0.005% (Xalatan);

b) travoprost 0.004% (Travatan);

c) bimatoprost 0.03% (Lumigan 0.3 mg/ml); and

d) unoprostone 0.15% (Rescula).

iv) Other compounds were available but were either used only for the treatment of acute glaucoma, or were older products, such as carbachol and pilocarpine, the use of which had been largely superseded by more modern drugs, certainly for first line treatment.

36. Many eye drops for the treatment of glaucoma were available in a range of concentrations of the active ingredients.

37. Combination therapy, typically with drugs from two or more different classes, was (and still is) used where necessary to achieve a high reduction in IOP.

38. The skilled ophthalmologist in March 2005 would consider that it was advantageous to have more choice in available glaucoma treatments, even if this did not result in any greater efficacy, since it was useful to have another medication to switch patients to in the event that they experienced tachyphylaxis with a particular drug (loss of efficacy due to resistance or tolerance).

PGAs

39. Initially, PGAs were the preferred class only for patients for whom beta-blockers were contra-indicated. By March 2005, however, they were increasingly being used as the first line treatment for all patients. This was because it was recognised that they had advantages over other drugs, in particular that they effectively lowered IOP and could be administered once daily. Together, this greatly improved patient adherence.

40. The consensus of opinion in 2005 was that latanoprost was the preferred PGA, even if it was more expensive than the alternatives. This was because it had been shown to be highly efficacious, typically lowering IOP by 25-32%, and had been found to be safe and well-tolerated over several years of use.

41. Although bimatoprost was technically a prostamide, and was administered in that form rather than in the form of a pro-drug such as an ester, as in the case of latanoprost and travoprost, it was regarded as being a member of the PGA class. While bimatoprost had superior efficacy in reducing IOP, typically by 27-33%, it was not used as a first line treatment in March 2005. Usually it was used as a second or third line treatment. This was because it had a worse side effect profile than the other PGAs, as explained below.

Side effects of PGAs

42. By March 2005, all of the PGAs used in the UK were known to be associated with the adverse effects of (i) conjunctival hyperaemia (or hyperemia), (ii) eyelash lengthening and (iii) hyperpigmentation of periorbital skin, lashes and the iris. The last two of these were rare, but hyperaemia was a more common side effect.

Hyperaemia

43. Hyperaemia is a general term that refers to the vasodilation and engorgement of blood vessels. Conjunctival hyperaemia manifests itself as "red eye".

44. Hyperaemia was more common with bimatoprost than with the other PGAs. In 2005 approximately 20-30% of patients using Lumigan 0.3 mg/ml experienced hyperaemia, which lasted for the duration of the treatment. The effect was so marked that an experienced clinician was often able to guess that a patient was using bimatoprost before referring to their medication history.

45. As a consequence, although 0.03% bimatoprost was efficacious and comfortable to use, many patients were unable to tolerate its side effects. It was well recognised by 2005 that hyperaemia could reduce patient adherence to PGA treatment. In a significant proportion of cases where patients discontinued bimatoprost, the primary reason was as a result of hyperaemia. This association of hyperaemia and bimatoprost became generally known within a few months after the drug was made available for use, and certainly by March 2005.

46. The skilled ophthalmologist in March 2005 would assume that the hyperaemia associated with Lumigan 0.3 mg/ml was caused by the active ingredient, although they would not be aware of the underlying mechanism. The skilled ophthalmologist would expect the hyperaemia associated with bimatoprost to be dose-dependent, because it was (and remains) a generally known pharmacological principle that drug effects are usually proportional to drug concentration, although the ophthalmologist would not know the details of that dose-dependency.

Formulation of eye drops

47. Eye drops can be formulated for single-use or multi-use containers. In 2005 multi-use containers were much more common than single-use ones.

48. A simple solution multi-use eye drop formulation for glaucoma in 2005 typically comprised:

    i) The active pharmaceutical ingredient.

    ii) A vehicle to act as a carrier for the drug and excipients. If the drug is dosed in very small quantities, the vehicle will also bulk out the formulation for ease of administration into the eye. Water was the most commonly used vehicle.

    iii) A preservative to maintain sterility and prevent microbial growth during the period of use. Topical eye formulations are administered directly to the eye and have to be sterile, because eye infections can have severe consequences. Preservatives are required for multi-use products in order to avoid the proliferation of microbial growth within the eye drop bottle. In March 2005 BAK was the leading preservative used in ophthalmic products.

    iv) A tonicity modifier to control the tonicity of the solution such that it is compatible with tear fluid. Tonicity refers to the osmotic pressure exerted by salts in aqueous solution. When such a solution is instilled into the eye, it mixes with tear fluid. The resulting osmotic pressure is dependent on the osmolality of the tears, as well as that of the formulation (and the amount of formulation itself). If the osmotic pressure is lower than 260 mOsm/kg or higher than 480 mOsm/kg, the formulation becomes an irritant. This induces reflex tearing and blinking and is likely to reduce the bioavailability of the drug in question. The optimal target in 2005 for an eye drop was 280-350 mOsm/kg, to match the osmolality of tear fluid. Commonly used tonicity modifiers in March 2005 included sodium chloride. It was generally understood that a 0.9% solution of NaCl would be isotonic.

    v) Buffering agents to control and maintain the pH of the solution such that it is compatible with tear fluid. The normal pH of tear fluid is 7.4. Ocular formulations are ideally formulated to have a similar pH to this, for example between 7.3 and 7.7, to avoid eye irritation, although sometimes the necessary pH of the formulation is outside of this range to ensure stability of the active ingredient. Tear fluid has only a limited buffering capacity and it is therefore common to include a buffer to maintain normal pH of the tear fluid. Phosphate buffers were commonly used.

BAK

49. BAK is a cationic surfactant. In March 2005 it was used in around two-thirds of commercial ophthalmic products (and is still commonly used today). It was used in a range of concentrations from 40 ppm to 200 ppm, with 100 ppm being the most common.

50. In March 2005 the following concentrations of BAK were used in commercially available PGA formulations:

    i) 50 ppm (Lumigan 0.3 mg/ml, bimatoprost);

    ii) 150 ppm (Travatan, travoprost);

iii) 150 ppm (Rescula, unoprostone);

iv) 200 ppm (Xalatan, latanoprost).

Techniques to increase ocular bioavailability

51. The skilled formulator would know in March 2005 that there were various techniques to try to increase the ocular bioavailability of a drug. These could be divided into two broad classes:

i) Increasing the pre-corneal residence time. This approach was based upon preventing drainage of the drug from the pre-corneal area, thereby allowing more time for it to penetrate the cornea. There were multiple methods for increasing pre-corneal residence time, including the use of viscosity enhancers, in-situ gels, inserts, bioadhesives and other methods.

ii) Increasing the amount of the drug which penetrated the cornea. This class further sub-divided into two categories:

a) Modifying the physicochemical properties of the drug, such as its lipophilicity or solubility, to improve its absorption across the cornea. This category included the use of a pro-drug, an ion-pairing agent or a cyclodextrin.

b) Use of a penetration enhancer to increase the permeability of the cornea. Such enhancers included surfactants, bile salts and calcium chelators.

The Patent

52. The specification begins at [0001] by stating that the invention relates to pharmaceutical compositions comprising bimatoprost, which is described at [0002] as a prostamide marketed commercially for the treatment of glaucoma and ocular hypertension. The specification goes on at [0003] to state that BAK is a preservative used in many commercial ophthalmic products to prevent microbial contamination in multi-use products, and that the commercially available bimatoprost eye drops contain 0.03% bimatoprost and 0.005% BAK. It then notes that several commercially available prostaglandin analogues use BAK as a preservative, including latanoprost (Xalatan), travoprost (Travatan), and unoprostone isopropyl (Rescula). The specification states that these all require significantly more BAK, from 150-200 ppm (i.e. 0.015-0.02%), to meet antimicrobial effectiveness tests in the United States and Europe.

53. There are consistory paragraphs corresponding to claims 1 and 12 at [0007]-[0008].

54. The specification discloses ranges of concentration of bimatoprost and BAK for use in the invention at [0010] and [0011] respectively. This is followed by a discussion of suitable excipients at [0012]-[0017], including chelating agents such as ethylenediaminetetra-acetic acid (EDTA), buffers, viscosity-enhancing agents and tonicity agents such as sodium chloride.

55. A number of embodiments of the invention with various concentrations of bimatoprost and BAK at pH 7.3 or 7.4 are described at [0022]-[0036]. New claim 18 is based on the embodiment described in [0022]. Five examples are then described, although in reality they amount to two experiments.

Examples 1 and 2

56. This defines formulations with varying amounts of bimatoprost, BAK and/or D-α-tocopheryl polyethylene glycol 1000 succinate ("TPGS"), together with standard excipients. The Patent does not disclose what TPGS is, but the skilled formulator would recognise it as a non-ionic surfactant.

57. Six formulations are listed in Table 1. Formulation 1 contains 0.03% bimatoprost and 50 ppm BAK and is therefore equivalent to the commercially available Lumigan 0.3 mg/ml product. It is labelled as "Control". Formulation 2 contains 0.03% bimatoprost and 200 ppm BAK. Formulations 3 to 6 all contain various amounts of TPGS, 0.03% bimatoprost and no BAK.

58. Example 2 describes an *in vivo* study in rabbits which used the formulations of Example 1 to determine the effect of BAK and TPGS on ocular absorption of bimatoprost. The specification explains at [0039] that, due to extensive metabolism of bimatoprost in rabbit eyes, its parent acid was used as a surrogate for determining bimatoprost ocular absorption.

59. The results of the study are set out in Table 2 and Figure 1. These show that increasing the concentration of BAK from 50 ppm to 200 ppm results in an increase in the concentration of bimatoprost acid in the aqueous humour from 51.0 (±9.4) ng/mL to 87.2 (±19.0) ng/mL. The specification states at [0040] that this is a 57% higher aqueous humour bimatoprost concentration (although as a matter of arithmetic the correct figure is 71%).

60. The specification also notes in [0040] that, compared to the bimatoprost control, the formulations containing TPGS resulted in decreased bimatoprost permeability. In contrast, it is said, "formulations with higher BAK resulted in higher permeability" (although only one formulation with higher BAK was tested).

Examples 3 and 4

61. Example 3 lists 14 formulations which were prepared with various concentrations of bimatoprost and/or BAK and/or EDTA. These are set out in Table 3. As with Example 1, 0.03% bimatoprost with 50 ppm BAK (i.e. the commercially available product) is listed as the control (Formulation A).

62. The formulations described in Example 3 were used in Example 4. Example 4 describes an *in vitro* study to determine the effect of BAK and EDTA on bimatoprost permeability across rabbit corneal epithelial cell layers. The results of this are set out in Figure 2. Slightly oddly, the specification does not comment on the results. It can be seen from Figure 2, however, that, in general, the results show that the higher the BAK concentration, the more bimatoprost is able to permeate across the corneal epithelial cells.

Example 5

63. Example 5 concerns Formulation J from Table 3. This contains 0.015% bimatoprost, 125 ppm BAK and 0.015% EDTA. The specification states in [0044] that a single drop of formulation J "is administered" once daily to the eye of a person suffering from glaucoma. After "a few hours", IOP "drops more" and "less hyperaemia is observed than would be observed for Formulation A". Given the use of the present tense (compared to the past tense in Examples 1-4) and the absence of any data, this appears to be a prophetic example. In any event, even if it is a record of an actual treatment, the experts were agreed that no conclusions as regards the general population can be derived from a single patient.

What is not in the Patent

64. There are no data in the Patent concerning the incidence of hyperaemia, or as to safety or tolerability more generally, with any of the claimed formulations. Nor are there are any data comparing the efficacy of any of the claimed formulations with the efficacy of Lumigan 0.3 mg/ml. More specifically, there are no data concerning these factors with a formulation falling within new claim 18.

The claims

65. The only claims relied upon by Allergan are granted claims 1, 5 and 12 and new claim 18. These are as follows:

> "1. A composition comprising from 0.005% to 0.02% bimatoprost by weight and from 100 ppm to 250 ppm benzalkonium chloride, wherein said composition is an aqueous liquid which is formulated for ophthalmic administration.
>
> 5. The composition of claim 1 wherein the concentration of bimatoprost is from 0.01% to 0.02%.
>
> 12. The composition of any preceding claim for treating glaucoma or intraocular hypertension in a mammal.
>
> 18. A composition comprising 0.01% bimatoprost, 0.02% benzalkonium chloride, 0.0268% sodium phosphate dibasic heptahydrate, 0.014% citric acid monohydrate, 0.81% sodium chloride, and water, wherein the pH is 7.3."

66. There is no issue as to the interpretation of the claims. It is common ground that they do not include any requirements as to safety or tolerability or efficacy compared to Lumigan 0.3 mg/ml.

The skilled team

67. It is common ground that the skilled team to whom the Patent is addressed would comprise an ophthalmologist with a particular interest in and experience of treating glaucoma ("the skilled ophthalmologist"), and a formulator with expertise in the field of ophthalmic formulation ("the skilled formulator"). The skilled team would most

likely be employed or engaged by a pharmaceutical company, but could be based in academia.

68. In developing a new formulation of an existing drug, the skilled ophthalmologist would advise on the medical needs, the doses to investigate and the overall efficacy levels and safety required. The skilled formulator would do everything else: they would understand the possible avenues of reformulation and their feasibility and would devise the formulation.

Common general knowledge

69. There is little, if any, dispute that everything I have set out in the technical background section of this judgment was part of the common general knowledge of one or both members of the skilled team, and in any event that is my finding. There was, however, a certain amount of dispute as to the common general knowledge of the members of the skilled team concerning BAK beyond the matters stated above.

CGK of the skilled ophthalmologist

70. Allergan contend that there was a move away from the use of BAK by March 2005. The evidence of the experts establishes that there was indeed an increasing awareness by that date that it was desirable not to use preservatives such as BAK if it was not necessary, and hence an increase in the availability of preservative-free single use formulations. This is of little relevance, however, since as noted above the majority of ophthalmic formulations were preserved with BAK.

71. Dr Diamond and Prof Morgan were agreed that the skilled ophthalmologist would consider the level of BAK used with latanoprost to be safe for the majority of patients, since eight years' use of latanoprost had shown it to be well-tolerated. Allergan appeared at one stage to be contending that the skilled ophthalmologist would be concerned as to whether 200 ppm of BAK would be safe with a PGA other than latanoprost, but this contention was not pursued in closing submissions. In any event, Dr Diamond accepted that there would be no concern that BAK would have a different effect with a different active ingredient. As counsel for the Defendants pointed out, this is confirmed by the fact that the safety of Xalatan was the rationale used by Allergan to support the safety of 200 ppm BAK with bimatoprost (see further below).

72. It was common ground between Dr Diamond and Prof Morgan that it was known that, despite BAK being a common preservative, some patients would exhibit or develop sensitivity to it, resulting in discomfort, irritation or hyperaemia. Counsel for Allergan suggested to Prof Morgan that the skilled ophthalmologist would not know whether or not the presence of BAK in a PGA formulation exacerbated hyperaemia. This was not a suggestion which had been advanced by Dr Diamond, however, and Prof Morgan explained that the fact that the PGA with the highest level of BAK (latanoprost) had the lowest incidence of hyperaemia was compelling evidence that it was the active ingredient that was the cause and not BAK. Moreover, Dr Diamond and Prof Morgan agreed that bimatoprost was thought to be the cause of the hyperaemia associated with Lumigan 0.3 mg/ml.

73. The principal area of dispute is whether it was common general knowledge that BAK enhanced the corneal permeability, and hence bioavailability, of ophthalmic drugs.

74. Prof Morgan's opinion was that it was common general knowledge that BAK enhanced the corneal penetration of some drugs. His opinion is supported by four textbooks:

i) *Adler's Physiology of the Eye: Clinical Application* edited by Kaufman and Alm (10th ed, 2003) was a very well-known textbook. It was used as the main physiology/pharmacology reference for Part 1 of the Primary Fellowship of the Royal College of Surgeons. This states at page 96 (footnotes omitted):

> "**CORNEAL PHARMACOLOGY**
>
> **Factors Affecting Drug Penetration**
>
> …
>
> The inclusion of surfactants and detergents, such as benzalkonium chloride (BAK) or Tween 20 in topical ocular medications … may also improve drug penetration through the outer epithelial barrier, in addition to the preservative effect inherent to these agents.
>
> **Effects of Preservatives Used in Ophthalmic Preparations**. … The most commonly used preservative is BAK. … The antibacterial action of BAK is based on the detergent property of the compound, which acts to break down bacterial cell walls. These characteristics of a preservative also render the corneal epithelium and endothelium susceptible to damage when they are exposed to these agents.
>
> The effects of BAK on the corneal epithelium have been studied extensively. Application of a drop containing 0.01% BAK to the cornea causes an immediate, measurable increase in the permeability of the cornea to fluorescein. …. "

ii) Ophthalmology Monograph 13 *Glaucoma Medical Therapy: Principles and Practice* edited by Netland and Allen (Foundation of the American Academy of Ophthamology, 1999) states at pages 5, 8 and 10 (footnotes omitted):

> "**BIOAVAILABILITY IN OCULAR COMPARTMENTS**
>
> …
>
> **Drug Absorption**
>
> …
>
> Transcorneal movement [of drugs] can be increased by changing the barrier properties of the corneal epithelium, by

applying an anaesthetic, by preservatives in topical medications, or after damaging the epithelium.

…

DRUG FORMULATION

… In addition to the active drug, ophthalmic solutions or suspensions contain other ingredients to control various characteristics of the formulation, such as the buffering and pH, osmolality and tonicity, viscosity, and antimicrobial preservation. Although these ingredients are listed as inactive, they can affect the permeability of the drug across the ocular surface barrier and alter the therapeutic effectiveness of the drug.

…

Preservatives

Common preservatives in ophthalmic preparations are quaternary cationic surfactants such as benzalkonium chloride ... It has been shown that preservatives used in ophthalmic solutions can be toxic to the ocular surface following topical administration and can enhance the corneal permeability of various drugs."

iii) *Duane's Clinical Ophthalmology* edited by Tasman and Jaeger (2004 edition) states in Chapter 22 at page 9 (footnotes omitted):

"**SURFACTANTS**. Detergents are added to ocular solutions for several reasons: they increase the solubility of drugs that are relatively hydrophobic; they may act as preservatives because of their antibacterial activity; or they may be added for their ability to partially break down the barrier presented by the corneal epithelium, thereby enhancing drug penetration and bioavailability. Benzalkonium chloride is the detergent most commonly used as a preservative in ophthalmic solutions. It is a cation and usually used in low concentrations (e.g., 1/10,000). … Smolen and coworkers reported that the bioavailability of carbachol was enhanced significantly in the presence of 1/5000 benzalkonium chloride. Rabbits given a 0.1% carbachol solution with 1/2500 benzalkonium chloride obtained as much miosis as if given a 2% carbachol solution without surfactant. Tonjum has used the electron microscope to study the effect of benzalkonium chloride on rabbit corneal epithelium. He found that this surfactant broke down the tight junctions of the epithelial cells and allowed penetration of horseradish peroxidase. Similar increases in drug penetration have been reported by others using this and other … ionic detergents."

iv) *Oxford Textbook of Ophthalmology Volume 1* edited by Easty and Sparrow (1999), which Dr Diamond contributed to, states in chapter 1.4 at page 59:

> "Benzalkonium chloride, a preservative widely used because of its microbial activity at a wide range of pH, can cause significant corneal and conjunctival irritation and epithelial erosions at or near clinical concentrations (0.01-0.04 per cent). Preservatives often increase corneal epithelial permeability, allowing for significant enhancement of drug bioavailability. These potential advantages must be weighed against their potential tissue toxicity. In the case of benzalkonium chloride, the use of low concentrations (> 0.01 per cent) appears to offer an acceptable balance between inhibiting microbial growth and limiting toxicity."

75. Dr Diamond's evidence was that, although he accepted that he had probably read the passage in *Adler's* when qualifying, he had forgotten it since then. Moreover, none of four colleagues at BEH whom he had asked remembered the statement that BAK can improve corneal penetration. He accepted, however, that the skilled ophthalmologist who wanted to know about the effects of BAK would know that *Adler's* was a ready place to turn to for this information. The result would be the same if they consulted one of the other textbooks.

76. Accordingly, I conclude that it was part of the skilled ophthalmologist's common general knowledge that BAK could act as a penetration enhancer as well as having a preservative effect. Even if I am wrong about that, it would be obvious for a skilled ophthalmologist engaged in a project involving formulations containing BAK to ascertain that information.

77. It should be noted that, although the textbooks do not suggest that BAK will always have this effect, they do not identify classes of drug for which it is effective and classes for which it is not. Rather, the message which is conveyed is that it is a general property of BAK.

CGK of the skilled formulator

78. Again, the principal area of dispute is whether it was common general knowledge that BAK enhanced the corneal penetration, and hence bioavailability, of ophthalmic drugs.

79. Prof Alany's opinion was that it was common general knowledge that BAK enhanced the corneal penetration of a wide range of ophthalmic drugs. His opinion is supported by considerable number of articles and reviews dating back to 1944 and textbooks which were current in March 2005. It is sufficient to refer to five textbooks:

i) *Ophthalmic Drug Delivery Systems* edited by Mitra (2nd ed, 2003). It is common ground that this textbook is one that the skilled formulator would be familiar with and have access to. Chapter 7 is entitled "Ocular Penetration Enhancers". It sets out a "summary of ophthalmic penetration enhancers" in Table 4. The first preservative listed is BAK, and it records that BAK at varying concentrations has been shown to enhance the penetration of

prostaglandin F2α, pilocarpine, dexamethasone, tilisolol, FD-4, FD-10, atenolol, timolol, levobunolol, betaxolol, fluorescein, carbachol and titmolol.

ii) *Physicochemical Principles of Pharmacy* by Florence and Attwood (3rd ed, 1998). Prof Kompella agreed that this was a well-respected textbook. It states at page 421:

> "Some ingredients of eye medications may increase the permeability of the cornea. Surface-active agents are known to interact with membranes to increase the permeability: benzalkonium chloride has surfactant properties and may well have some effect on corneal permeability, although its primary purpose is as a bacteriostat and bactericide."

iii) *Biopharmaceutics of Ocular Drug Delivery* edited by Edman (1993). Prof Kompella appeared to accept that the skilled formulator would have access to this book. Chapter 3 is entitled "The Effects of Preservatives on Corneal Permeability of Drugs". It discusses BAK at some length at pages 46-48. It is sufficient to note the following passages on page 46 (footnotes omitted):

> "Cationic surfactants tend to act on microbes indiscriminately by solubilizing cell membranes, while anionic surfactants may act in different ways. In ophthalmic practice one cationic detergent, benzalkonium chloride (BAK), is widely used as a preservative because of its bacteriostatic and bacteriocidal efficacy at a wide range of vehicle pH. Because of its mode of action, it is not surprising that BAK also indiscriminately affects corneal cell membranes.
>
> …
>
> BAK influence on rabbit epithelial permeability has been demonstrated for fluorescein, pilocarpine, prednisolone acetate, chloramphenicol, carbachol, dexamethasone, and sodium chloride, and for prostaglandin F2α in pig epithelium. BAK caused dose-dependent increases in epithelial sulforhodamine B permeability of corneas of freshly killed mice."

The chapter also states in its conclusions at page 52 (footnotes omitted):

> "Wherever preservatives are employed their use must be evaluated on a risk to benefit ratio. The most obvious benefit of preservatives is that of acting as a bactericide for the solution to prevent microbial growth should the container come in contact with a potentially contaminating surface during drug application. … The next, but less evident, benefit of certain preservatives is to increase corneal epithelial permeability. This factor, which may occur because of the bactericidal action of the preservative, may play an important role in drug bioavailability since the latter has corneal penetration as a major contributing factor. BAK, for example, is an excellent

> bactericide that also induces increased drug permeation across the cornea, and because of the lack of penetration of this compound beyond the corneal epithelium, BAK has a markedly diminished potential toxicity to internal ocular structures. Use of this compound at concentrations less than 0.01% appears to be appropriate to satisfy bactericidal, toxicological, and pharmaceutical considerations."

iv) *Modern Pharmaceutics* edited by Banker and Rhodes (2nd ed, 1990). Prof Kompella accepted that this is another book that the skilled formulator in industry would be familiar with. It states at page 551 (footnotes omitted):

> "The usual concentration of benzalkonium chloride used in topical eyedrops is 0.01%, with a range of 0.004 to 0.02%. A 0.03% solution has been used as a penetration enhancer for carbachol in addition to its preservative activity. However, lower concentrations of benzalkonium chloride have been found to enhance corneal penetration of compounds."

v) *Havener's Ocular Pharmacology* edited by Mauger and Craig (6th ed, 1994). This states at pages 477 and 480:

> "One of the most popular cationic detergents is benzalkonium chloride. This drug may be used in ophthalmology for the preservation of eye drops … and to enhance corneal penetration of drugs.
>
> …
>
> Since the introduction of carbachol in benzalkonium chloride in 1942, these 'wetting agents' are known to increase corneal penetration of drugs. This was considered to be a desirable effect that enhanced therapy and was therefore to be sought. The reason for enhanced penetration must be damage to the epithelial cells. Fortunately, they grow back so rapidly as to be completely replaced every 3 days, so damage to them is relatively inconsequential or at least transitory."

80. Prof Kompella's evidence in his first report was that it was not well known that BAK was a penetration enhancer and disputed that it was an obvious candidate to use for this purpose. He qualified this by saying that it was generally known that BAK could form ion-pairs with negatively charged active ingredients and could form complexes with certain active compounds, both of which could improve permeation through the cornea, but concluded that BAK could have a positive, negative or no effect on bioavailability depending on a large number of other factors.

81. In his second report, Prof Kompella maintained this position, but added that a skilled formulator who was considering the properties of BAK and consulted Edman would go to the underlying references, and that one of those references, Camber and Edman, suggested that bimatoprost, as a moderately lipophilic drug, was more likely to have its corneal penetration inhibited than enhanced by BAK.

82. As Prof Kompella had to accept in cross-examination, however, the textbooks and articles convey the general message that BAK enhances corneal penetration. Indeed, the same message is conveyed by two of Prof Kompella's own publications. First, "Barriers to Drug Transport in Ocular Epithelia" by Kompella and Lee in *Transport Processes in Pharmaceutical Systems* edited by Amidon *et al* (2000) states under the heading "Penetration Enhancers" at page 349 and 350 (footnotes omitted):

> "Chelators, bile salts, surfactants, and fatty acids are some example of penetration enhancers that have been widely tested.
>
> … there are reports on enhancement of ocular drug absorption by bile salts, surfactants and chelators."

While this does not specifically refer to BAK, BAK is a surfactant.

83. Secondly, Kompella *at al*, "Recent advances in ophthalmic drug delivery" *Ther Deliv*, 1(3), 435-456 (2010) states at page 11:

> "Despite extensive research in the area of penetration enhancers to overcome epithelial barriers, no clinical ophthalmic formulation relies directly on the penetration-enhancing properties of its excipients. However, the fact that several ophthalmic formulations contain benzalkonium chloride and/or EDTA as preservatives is noteworthy. Both these excipients are well known to alter biological membranes, thereby enhancing drug permeability [89-91]. For a comprehensive review on the mechanisms of action of penetration enhancers, the readers are referred to an article by Lee *at al* [92]."

Although this review was published in 2010, references 89-92 all pre-date 2005. I would add that all four references, and both of these publications by Prof Kompella, were co-authored by Professor Vincent Lee, a well-known figure in the field who supervised Prof Kompella's PhD work.

84. I have dealt with Prof Kompella's reliance upon Camber and Edman in paragraph 10 above. As noted there, it was flawed. In any event, it was not put to Prof Alany that Camber and Edman was common general knowledge or that it would be obvious for the skilled formulator to refer to it.

85. Counsel for Allergan accepted in his closing submissions that it was common general knowledge that BAK could enhance corneal penetration in some circumstances, but submitted that it had not been established that BAK was known to be practically useful as a penetration enhancer. I do not accept this submission. In my judgment the evidence shows that it was common general knowledge that BAK was generally effective as a penetration enhancer. It is true that there is no evidence that it was included in ophthalmic formulations purely for that reason. It was included because it was a preservative; but it was well understood that it had the additional benefit of enhancing corneal penetration for a wide range of drugs. This was a concentration-dependent effect.

86. Two issues were raised concerning the safety of BAK. First, Prof Kompella suggested that there might be a difference between the safety of 200 ppm BAK in a latanoprost formulation and in a formulation of a different drug, but he was unable to point to any evidence that a particular level of BAK which had been shown to be safe in a formulation of one active ingredient had been found to be unsafe with a different active ingredient. When it was put to him that, if the skilled ophthalmologist had no concerns about using 200 ppm BAK, the skilled formulator would not differ from the skilled ophthalmologist, Prof Kompella's answer was that it would depend on whether safety had been proven in a clinical trial. He did not give any cogent reason as to why the skilled formulator should take a different view from that of the skilled ophthalmologist, however.

87. Secondly, it was common ground between Prof Kompella and Prof Alany that it was best practice to minimise the amount of preservatives such as BAK unless there was good reason not to do so. This was reflected in regulatory guidelines such as the European Medicines Agency's *Note for Guidance on the Inclusion of Antioxidants and Antimicrobial Preservatives in Medicinal Products* (July 1997), which states at page 3:

> "The concentration used must be justified in terms of efficacy and safety, such that the minimum concentration of preservative is used which gives the required level of efficacy.
>
> …
>
> The safety of the antioxidant or preservative should be supported by bibliographic and/or experimental data."

88. The only evidence as to the minimum level of BAK which is required to preserve formulations of bimatoprost is the fact that Lumigan 0.3 mg/ml contained 50 ppm.

89. Finally, there is a point concerning bimatoprost which was not shown to be common general knowledge, but which it is convenient to deal with here. No experimentally determined partition coefficient for bimatoprost had been published by March 2005. It is common ground, however, that the skilled formulator could readily calculate a predicted value using one of a number of well-known software packages, and that it would be obvious to do so. It is also common ground that the predicted value would be logP 3.2, which means that bimatoprost is moderately lipophilic. The skilled formulator would appreciate that 3.2 was higher than the top of the optimum range for corneal permeability, but not greatly so.

Laibovitz

90. Laibovitz describes a Phase II dose-ranging study conducted on bimatoprost. It is a 30 day, randomised, investigator-masked clinical trial involving 100 patients comparing the safety and efficacy of bimatoprost with timolol in patients with ocular hypertension or glaucoma. Bimatoprost was given at doses of 0.003%, 0.01% or 0.03% once daily for three weeks, then twice daily for one week. Timolol was given at 0.5% twice daily for four weeks. One group received vehicle only as a control. There were twenty patients in each group. Laibovitz states that the formulations used

were non-preserved since "no preserved formulations were available at the time the study was conducted". No other information about the formulations is provided.

91. The results of the trial may be summarised as follows:

    i) Figure 1 plots the mean change from baseline IOP with the various formulations studied and shows that both the 0.01% and 0.03% bimatoprost doses caused a prolonged and statistically significant drop in IOP when compared to timolol.

    ii) Figure 2 plots the mean percentage change from baseline IOP on day 14. 0.03% bimatoprost shows the greatest IOP lowering effect, namely 29.6%. The 0.01% dose lowered IOP by 20.7%. Both of these figures were statistically significantly different to the figure for timolol, which was 12.9%. The 0.003% dose lowered IOP by 13.1%, which was not statistically significantly different to timolol.

    iii) Table 2 shows that 0.03% bimatoprost administered once daily for 21 days caused a mean drop in IOP of 7.2 to 8.2 mm Hg and twice daily for a further 7 days caused a mean drop in IOP of 7.7 to 8.7 mm Hg. 0.01% bimatoprost administered once daily for 21 days caused a mean drop in IOP of 5.4 – 6.0 mm Hg and twice daily for a further 7 days caused a mean drop in IOP of 5.6 to 5.8 mm Hg. Timolol administered twice daily for 28 days caused a mean drop in IOP of 3.4 to 3.9 mm Hg.

92. The authors note at page 999 that the mean reductions in IOP achieved with timolol were less than anticipated (the reductions typically reported being 20-25%), and suggest that this may have been because patients were not excluded for previous use of timolol.

93. Laibovitz reports at page 998 that the overall incidence of adverse side effects was minimal for all of the treatment groups. The most frequent adverse event reported was conjunctival hyperaemia, which was reported in 1 (5%), 3 (15%) and 1 (5%) of the 20 patients in the 0.003%, 0.01% and 0.03% bimatoprost groups respectively. There were no reports of hyperaemia in the vehicle or timolol groups. The differences between the bimatoprost rates and the timolol rate were not statistically significant.

94. Laibovitz also reports at page 998 "a minor dose-related increase in the degree of conjunctival hyperaemia (generally a trace to a mild increase during the once daily phase)" in the bimatoprost groups. Hyperaemia was assessed on a five-point scale, but there is no indication that comparative photographs were used for this purpose.

95. Laibovitz concludes at page 1000 that "although all 3 concentrations and both dosing regimens tested were effective and had an acceptable safety profile, the 0.03% concentration of [bimatoprost] instilled topically once in the evening had the most advantageous overall safety profile … Further clinical evaluation of 0.03% [bimatoprost] given once daily for long-term management of glaucoma and ocular hypertension is warranted."

Obviousness

The law

96. The Supreme Court has recently reviewed the law as to obviousness in *Actavis Group PTC EHC v ICOS Corp* [2019] UKSC 15. The overall tenor of the judgment of Lord Hodge, with whom the other members of the Court agreed, is to confirm the approach which had previously been adopted by the courts to this question. For present purposes, it is sufficient to note five points.

97. First, at [60] and [93]-[96] Lord Hodge endorsed, while not mandating, the use of the structured approach set out in *Windsurfing International Inc v Tabur Marine (Great Britain Ltd* [1985] RPC 59 as reformulated in *Pozzoli SPA v BDMO SA* [2007] EWCA Civ 588, [20007] FSR 37 at [33].

98. Secondly, at [63] Lord Hodge endorsed, while emphasising that it was not exhaustive, the statement of Kitchin J (as he then was) in *Generics (UK) Ltd v H Lundbeck A/S* [2007] EWHC 1040 (Pat), [2007] RPC 32 at [72]:

> "The question of obviousness must be considered on the facts of each case. The court must consider the weight to be attached to any particular factor in the light of all the relevant circumstances. These may include such matters as the motive to find a solution to the problem the patent addresses, the number and extent of the possible avenues of research, the effort involved in pursuing them and the expectation of success."

99. Thirdly, at [65] Lord Hodge agreed that it was relevant to consider whether something was "obvious to try", saying that "[i]n many cases the consideration that there is a likelihood of success which is sufficient to warrant an actual trial is an important pointer to obviousness". He nevertheless endorsed the observation of Birss J at first instance that "some experiments which are undertaken without any particular expectation as to result are obvious".

100. Fourthly, at [69] Lord Hodge said that "the existence of alternative or multiple paths of research will often be an indicator that the invention … was not obvious", but nevertheless endorsed the statement of Laddie J in *Brugger v Medic-Aid Ltd (No 2)* [1996] RPC 645 at 661:

> "[I]f a particular route is an obvious one to take or try, it is not rendered any less obvious from a technical point of view merely because there are a number, and perhaps a large number, of other obvious routes as well."

101. Although Lord Hodge did not explicitly make the point, it is implicit in his endorsement of this statement that it remains the law that what matters is whether the claimed invention is obvious from a technical point of view, not whether it would be commercially obvious to implement it.

102. Fifthly, at [70] Lord Hodge confirmed that the motive of the skilled person was a relevant consideration. As he put it:

> "The notional skilled person is not assumed to undertake technical trials for the sake of doing so but rather because he or she has some end in mind. It is not sufficient that a skilled person could undertake a particular trial; one may wish to ask whether in the circumstances he or she would be motivated to do so. The absence of a motive to take the allegedly inventive step makes an argument of obviousness more difficult."

Assessment

103. In closing submissions the parties sensibly focussed on the obviousness or otherwise of new claim 18. It is common ground that the inventive concept of claim 18 is a formulation of 0.01% bimatoprost with 0.02% BAK (i.e. 200 ppm) for treating glaucoma; it is not suggested by Allergan that the other excipients and the pH figure recited in claim 18 are anything other than conventional. It is also common ground that the key difference between claim 18 and Laibovitz is that, whereas Laibovitz discloses the use of 0.01% bimatoprost to treat glaucoma, it does not disclose the use of 0.02% BAK.

104. The Defendants' case is straightforward. It starts from the proposition that the skilled ophthalmologist would be interested in reducing the incidence of conjunctival hyperaemia observed with Lumigan 0.3 mg/ml. I do not understand Allergan to dispute this proposition, but in any event Dr Diamond and Prof Morgan were agreed on it.

105. The skilled ophthalmologist would see from Laibovitz that 0.01% bimatoprost was reported to lower IOP by 20.7%, which the skilled ophthalmologist would regard as sufficient to be clinically useful for the treatment of glaucoma and ocular hypertension. The skilled ophthalmologist would expect that a lower dose of bimatoprost than 0.03% would reduce the incidence of hyperaemia, but would note that the quality of the hyperaemia data reported in Laibovitz was poor. As Dr Diamond and Prof Morgan agreed, there are two problems with Laibovitz in this respect. First, the methodology used for the assessment of hyperaemia did not accord with best practice, since it did not involve taking photographs of the patients' eyes and comparing them to sample pictures. Secondly, the number of patients meant that the study was statistically underpowered.

106. An obvious course would therefore be to repeat the study with a better methodology for recording and scoring hyperaemia and more patients in order to generate better hyperaemia data and to confirm the IOP lowering efficacy of the bimatoprost doses, and in particular the 0.01% dose. Again, I do not understand Allergan to dispute this, but in any event Dr Diamond and Prof Morgan were agreed on this point.

107. Allergan contend that the cost of repeating Laibovitz would be "enormous". I do not accept this. It would not require a Phase III trial, but only a better designed and suitably powered Phase II trial (which is what Allergan in fact did). In any event, the cost is not a relevant factor to the assessment of obviousness, since it does not bear upon whether the step would be obvious from a technical point of view. I would add that another obvious course would be to repeat just the 0.01% and 0.03% bimatoprost arms of Laibovitz, which would reduce the cost of the exercise.

108. The skilled ophthalmologist would ask the skilled formulator to produce formulations of bimatoprost for this purpose. The Defendants contend that it would be obvious to use a preserved formulation, and in particular a formulation preserved with BAK. Allergan dispute this. Counsel for Allergan accepted that it would be obvious in the light of Laibovitz to produce a formulation of 0.01% bimatoprost with 50 ppm BAK for a commercial product, but submitted that it would not be obvious to use 50 ppm BAK for the purpose of repeating Laibovitz because of the possibility that BAK would affect the incidence of hyperaemia.

109. In my judgment this is a hopeless argument. The question is whether the inclusion of BAK would be an obvious choice from a technical point of view. Laibovitz makes it clear that the only reason why preserved formulations were not used in the original study is because they were not available – it was not a deliberate decision for any scientific reason. When repeating Laibovitz, it would obviously be convenient to be able to use multi-use containers, which would require the use of a preserved formulation. Since BAK was the most commonly used preservative, it would be the obvious choice. For the reasons discussed above, the skilled team would think that the hyperaemia associated with Lumigan 0.3 mg/ml was due to the bimatoprost, and not to the BAK. Accordingly, they would have no reason not to include BAK when repeating Laibovitz. As Prof Alany pointed out, if they wanted to check whether BAK had any effect, it would be straightforward to include a BAK-only arm as a control.

110. When devising preserved formulations for this purpose, the skilled formulator would have the choice of either starting from the known Lumigan 0.3 mg/ml formulation containing 50 ppm BAK or devising a new formulation from scratch using general principles. The easiest course would be the former, but it would not make any difference to the result if the latter course were adopted. Again, I do not understand Allergan to dispute this, but in any event Prof Kompella and Prof Alany were agreed on the point.

111. The Defendants contend that the inclusion of anywhere from 50 ppm to 200 ppm BAK as a preservative would be obvious given the use of that range in the commercially available PGA eye drops. Allergan dispute this. Allergan contend that, even if they included preservative at all, the skilled team would not include more than the minimum level of BAK i.e. 50 ppm.

112. In my judgment the inclusion of anywhere from 50 ppm to 200 ppm BAK was an entirely obvious choice for the reasons given by Prof Alany. It was common general knowledge that BAK was generally used in the range from 40 ppm to 200 ppm. It was also common general knowledge that BAK was used in the range 50 ppm to 200 ppm in the commercially available PGA eye drops. While 200 ppm is more than the minimum necessary to achieve adequate preservation of bimatoprost, there was no technical, as opposed to regulatory, reason not to use more BAK than the minimum provided it was safe and tolerable. As discussed above, the skilled team would be satisfied that the inclusion of 200 ppm BAK was safe and tolerable. Furthermore, the skilled team would have no reason to think that the inclusion of 200 ppm BAK in either 0.01% or 0.03% bimatoprost would have any adverse impact on the efficacy of the bimatoprost. It is telling that, when Prof Kompella was asked whether, leaving regulatory issues aside, it would require invention to use 100 ppm BAK, he declined to comment. Thus he was unable to suggest any reason why it would require

invention. There is no reason to think that his position would have been any different with respect to 200 ppm.

113. In the alternative, even if it was not obvious to include 200 ppm BAK purely as a preservative, the Defendants contend that it would have been obvious to try to optimise the bioavailability of bimatoprost by using BAK's additional property as a corneal permeation enhancer. This would be particularly useful for the lower doses of bimatoprost, given that Laibovitz indicates that they are not as efficacious as the 0.03% dose. The skilled team would expect that increasing the level of BAK from 50 ppm to 200 ppm would not only be safe and tolerable, but also would be likely to enhance the corneal permeation of bimatoprost, and hence its bioavailability and efficacy. Allergan dispute this.

114. In my judgment the inclusion of 200 ppm BAK in the lower doses of bimatoprost in order to increase the bioavailability of bimatoprost was obvious to try when repeating Laibovitz, and the skilled team would have a good expectation of success. (If they wanted to check whether BAK was having this effect, a straightforward step would be to include both 50 ppm and 200 ppm arms.) Prof Alany's evidence to this effect was convincing, while Prof Kompella's only real reason for suggesting the contrary view was bimatoprost's lipophilicity, but that depended upon his misreading of Camber and Edman.

115. Accordingly, I conclude that it was obvious in the light of Laibovitz to make a formulation containing 0.01% bimatoprost and 0.02% BAK. It follows that new claim 18 would be invalid, as are all the granted claims of the Patent.

Secondary evidence

116. Allergan rely upon two pieces of secondary evidence as supporting their case of non-obviousness.

117. The first is that fact that Allergan used 50 ppm BAK when creating the Lumigan 0.3 mg/ml product following the Laibovitz study. The short answer to this is that the fact that 50 ppm BAK was obvious does not show that 200 ppm was not obvious.

118. The second is the evidence of Dr Chang concerning the making of the invention. Having regard to the clear conclusions I have reached on the basis of the primary evidence, I do not consider it necessary or profitable to consider this evidence in any detail. It is sufficient to say that I do not consider it persuasive for a number of reasons.

119. First, Dr Chang's ability to the speak to the issue was limited for the reasons explained above.

120. Secondly, the main thrust of his evidence was that Allergan considered a variety of other options before settling on 0.01% bimatoprost and 0.02% BAK. But the problem with this is that the Lumigan Enhancement Project was a wider one of considering potential reformulation generally, rather than simply reducing the incidence of hyperaemia experienced with Lumigan 0.3 mg/ml. Moreover, many of the other ideas were barely pursued, if at all. In any event, the existence of other options does not show that 0.01% bimatoprost and 200 ppm BAK was not obvious.

121. Thirdly, as noted above, the person who did the key experiments was Joan-En Chang-Lin. She was the person who was responsible for including 200 ppm BAK in the 020 study which formed the basis for Examples 1 and 2 in the Patent. It appears from the documentary evidence that she did so because she thought it would enhance corneal penetration. She had been part of Vincent Lee's lab and had published a paper on the penetration enhancing effect of BAK in 2002: Sholz *et al*, "Pilocarpine Permeability across Ocular Tissues and Cell Cultures: Influence of Formulation Parameters", *J Ocul Pharmacol & Ther*, 18(5), 455-468. This states at 456 (footnotes omitted):

> "BAC [i.e. BAK] and EDTA are widely utilized to preserve eye drops, in which BAC operates as by cationic detergent surface action … BAC and EDTA can be assumed as absorption promoters by destroying the integrity of the superficial cell layers of tissues … In the present study, the effect on the permeability due to the preservative concentration and the biological barrier was studied."

The conclusion was that in general BAK facilitated drug transport.

122. Furthermore, although Joan-En Chang-Lin was not one of the authors, a subsequent paper by authors from Allergan and elsewhere reporting on a longer study (Katz *et al*, "Twelve-Month, Randomiszed, Controlled Trial of Bimatoprost 0.01%, 0.0125% and 0.03% in Patients with Glaucoma or Ocular Hypertension", *Am J Ophthalomol*, 149(4), 661-671 (2010)) gave the same rationale at page 661:

> "Bimatoprost 0.01% is a new formulation that was developed with the goal of creating a formulation of bimatoprost that would maintain the IOP-lowering efficacy achieved with bimatoprost 0.03% and have an improved overall safety profile, particularly improved ocular surface tolerability. The strategy was to reduce the concentration of bimatoprost and increase the concentration of benzalkonium chloride (BAK), a commonly used preservative that also can increase the corneal penetration[15] and intraocular bioavailability of topically applied medication."

Although reference 15 was published in 2007, it cites pre-2005 references for this proposition.

123. Fourthly, Allergan contend that the team were surprised by the results of the 020 study. Even if others were surprised, which I am not convinced of, I see no reason to think that Joan-En Chang-Lin was. As for Dr Chang, he circulated a review article from 2002 (Abelson and Fink, "How to Handle BAK Talk", *Rev Ophthalmol*, 9(12), 52-54) which states at page 54 that BAK "can increase ocular permeability".

124. Fifthly, Allegan contend that there were concerns within Allergan as to the high levels of BAK. In fact, the documentary evidence shows that the use of 200 ppm BAK was not considered to be a concern. On the contrary, Allergan anticipated that the fact that it was used in Xalatan meant that it would be acceptable to the US Food and Drug Administration (as indeed turned out to be the case). The same justification is stated in Katz *et al* at page 669 (footnotes omitted):

> "Bimatoprost 0.01% contains the same 0.02% concentration of BAK as latanoprost 0.005%, which has been used safely in glaucoma treatment for many years."

Insufficiency

125. The Defendants only rely upon insufficiency as a squeeze on their obviousness case: the Defendants contend that, if the claimed inventions are not obvious, nothing in the Patent rendered them plausible. Having regard to my conclusions on obviousness, this contention falls away. Nevertheless, I should record that I agree with the Defendants that, if the use of 200 ppm BAK was not obvious because safety concerns would deter the skilled team from using that level of BAK with bimatoprost, there is nothing in the Patent to dispel such concerns.

Conclusion

126. The Patent is invalid.